

Listing of Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Original) A pharmaceutical carrier or excipient system useful for preparing a pharmaceutical formulation, the carrier or excipient system comprising:

a) a filler and disintegrant component comprising from about 5% to about 82% by weight of the pharmaceutical formulation, of which from about 4% to about 40% by weight of the total formulation comprises one or more pharmaceutically acceptable disintegrants;

b) optionally, a wetting agent comprising from about 0.2 to about 5% of the pharmaceutical formulation;

c) a lubricant comprising from about 0.2% to about 10% of the pharmaceutical formulation; and

d) optionally, a glidant comprising from about 0.1% to about 10% of the pharmaceutical formulation.

2. (Original) The pharmaceutical carrier or excipient system of Claim 1 further comprising from about 0.5% to about 15% by weight of an antioxidant.

3. (Original) The pharmaceutical carrier or excipient system of Claim 2 wherein the antioxidant is selected from ascorbic acid, sodium ascorbate, ascorbyl palmitate, or mixtures thereof.

4. (Original) A pharmaceutical composition comprising a pharmaceutically effective amount of an active pharmacological agent and carrier or excipient system, the carrier or excipient system comprising:

a) a filler and disintegrant component comprising from about 5% to about 82% by weight of the pharmaceutical formulation, of which from about 4% to about 40% by weight of the total formulation comprises one or more pharmaceutically acceptable disintegrants;

b) optionally, a wetting agent comprising from about 0.2 to about 5% of the pharmaceutical formulation;

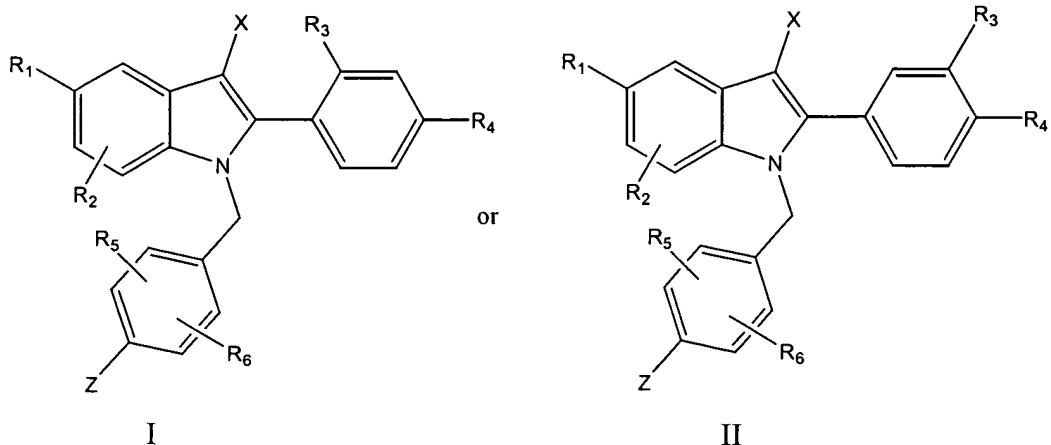
c) a lubricant comprising from about 0.2% to about 10% of the pharmaceutical formulation; and

d) optionally, a glidant comprising from about 0.1% to about 10% of the pharmaceutical formulation.

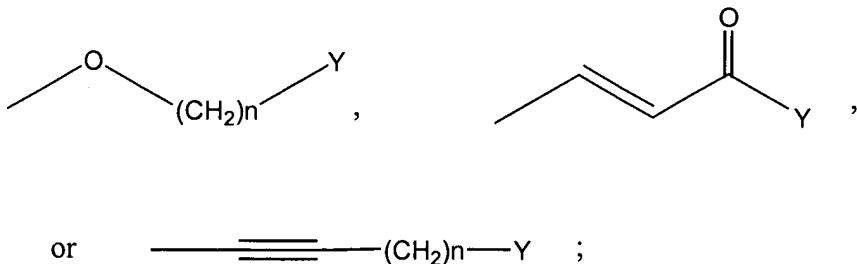
5. (Original) The pharmaceutical carrier or excipient system of Claim 1 further comprising from about 0.5% to about 15% by weight of an antioxidant.

6. (Original) The pharmaceutical carrier or excipient system of Claim 2 wherein the antioxidant is selected from ascorbic acid, sodium ascorbate, ascorbyl palmitate, or mixtures thereof.

7. (Original) A pharmaceutical composition of Claim 4 wherein the pharmacologically active agent is a compound of the formulae I or II:



wherein Z is a moiety selected from the group of:



wherein:

R₁ is selected from H, OH or the C₁-C₁₂ esters or C₁-C₁₂ alkyl ethers thereof, benzyloxy, or halogen; or C₁-C₄ halogenated ethers;

R₂, R₃, R₅ and R₆ are independently selected from H, OH or the C₁-C₁₂ esters or C₁-C₁₂ alkyl ethers thereof, halogens, or C₁-C₄ halogenated ethers, cyano, C₁-C₆ alkyl, or trifluoromethyl, with the proviso that, when R₁ is H, R₂ is not OH;

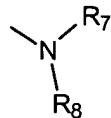
R₄ is selected from H, OH or the C₁-C₁₂ esters or C₁-C₁₂ alkyl ethers thereof, halogens, or C₁-C₄ halogenated ethers, benzyloxy, cyano, C₁-C₆ alkyl, or trifluoromethyl;

X is selected from H, C₁-C₆ alkyl, cyano, nitro, trifluoromethyl, halogen;

n is 1, 2 or 3;

Y is selected from:

a) the moiety:



wherein R₇ and R₈ are independently selected from the group of H, C₁-C₆ alkyl, or phenyl optionally substituted by CN, C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, -OH, -CF₃, or -OCF₃;

b) a five-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁C₄ alkyl)-, -N=, and -S(O)_m-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H-, -CN-, -CONHR₁-, -NH₂-, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, -NHSO₂R₁-, -NHCOR₁-, -NO₂, and phenyl optionally substituted with from one to three (C₁-C₄)alkyl groups;

c) a six-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁C₄ alkyl)-, -N=, and -S(O)_m-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H-, -CN-, -CONHR₁-, -NH₂-, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, -NHSO₂R₁-, -NHCOR₁-, -NO₂, and phenyl optionally substituted with from one to three (C₁-C₄)alkyl groups;

d) a seven-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁C₄ alkyl)-, -N=, and -S(O)_m-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H-, -CN-, -CONHR₁-, -NH₂-, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, -NHSO₂R₁-, -NHCOR₁-, -NO₂, and phenyl optionally substituted with from one to three (C₁-C₄)alkyl groups; or

e) a bicyclic heterocycle containing from 6-12 carbon atoms either bridged or fused and containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁C₄ alkyl)-, and -S(O)_m-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H-, -CN-, -CONHR₁-, -NH₂-, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, -NHSO₂R₁-, -NHCOR₁-, -NO₂, and phenyl optionally substituted with from one to three (C₁-C₄)alkyl groups;
or a pharmaceutically acceptable salt thereof.

8. (Original) The pharmaceutical composition of Claim 7 wherein in the compound of the formulae I or II:

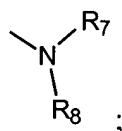
R₁ is selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, benzyloxy, or halogen;

R₂, R₃, R₅, and R₆ are independently selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, halogen, cyano, C₁-C₆ alkyl, or trihalomethyl; with the proviso that, when R₁ is H, R₂ is not OH;

R₄ is selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, benzyloxy, halogen, cyano, C₁-C₆ alkyl, or trihalomethyl;

X is selected from H, C₁-C₆ alkyl, cyano, nitro, trifluoromethyl, halogen;

Y is the moiety

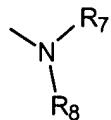


R₇ and R₈ are selected independently from H, C₁-C₆ alkyl, or combined by -(CH₂)_p, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄), -NH₃, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, -NHSO₂(C₁-C₄), -NHCO(C₁-C₄), and -NO₃;

or a pharmaceutically acceptable salt thereof.

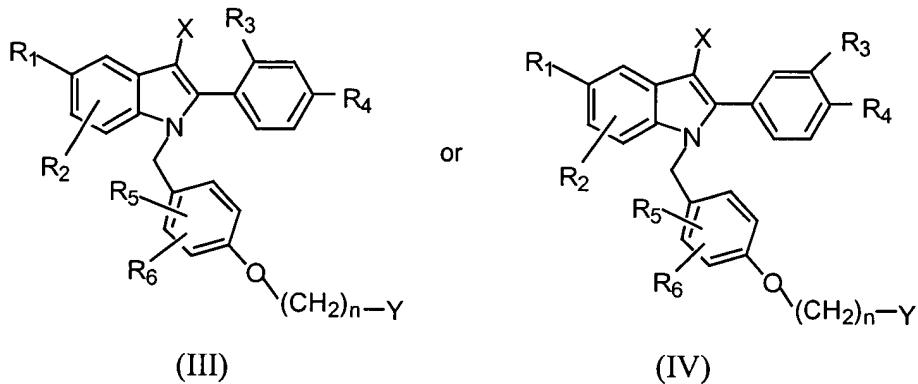
9. (Original) The pharmaceutical formulation of Claim 8 wherein, in the compound of the formulae I or II, the ring formed by the combination of R₇ and R₈ by -(CH₂)_p is selected from aziridine, azetidine, pyrrolidine, piperidine, hexamethyleneamine or heptamethyleneamine.

10. (Original) The method of Claim 7 utilizing a compound of the formulae I or II, wherein R₁ is OH; R₂ - R₆ are as defined in Claim 1; X is selected from the group of Cl, NO₂, CN, CF₃, or CH₃; and Y is the moiety



and R₇ and R₈ are concatenated together as -(CH₂)_r-, wherein r is an integer of from 4 to 6, to form a ring optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄)alkyl, -NH₂, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, and -NO₂; or a pharmaceutically acceptable salt thereof.

11. (Original) A pharmaceutical composition of Claim 4 wherein the active pharmacological agent is a compound of the formulae (III) or (IV):



wherein the substituents R₁, R₂, R₃, R₄, R₅, R₆, n, X, and Y are as defined in Claim 7, or a pharmaceutically acceptable salt thereof.

12. (Original) A pharmaceutical composition of Claim 11 wherein:

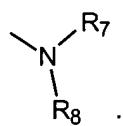
R₁ is selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, benzyloxy, or halogen;

R₂, R₃, R₅, and R₆ are independently selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, halogen, cyano, C₁-C₆ alkyl, or trihalomethyl, preferably trifluoromethyl, with the proviso that, when R₁ is H, R₂ is not OH;

R₄ is selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, benzyloxy, halogen, cyano, C₁-C₆ alkyl, or trihalomethyl;

X is selected from H, C₁-C₆ alkyl, cyano, nitro, trifluoromethyl, halogen;

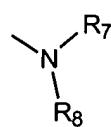
Y is the moiety



R₇ and R₈ are selected independently from H, C₁-C₆ alkyl, or combined by -(CH₂)_p-, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄), -NH₃, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, -NHSO₂(C₁-C₄), -NHCO(C₁-C₄), and -NO₃;

or a pharmaceutically acceptable salt thereof.

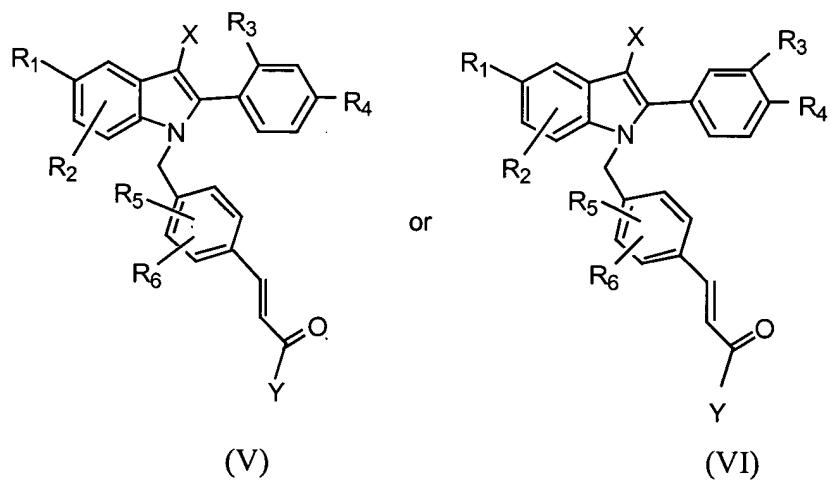
13. (Original) A pharmaceutical composition of Claim 11 wherein R₁ is OH; R₂ - R₆ are as defined above; X is selected from the group of Cl, NO₂, CN, CF₃, or CH₃; and Y is the moiety



and R₇ and R₈ are concatenated together as -(CH₂)_r-, wherein r is an integer of from 4 to 6, to form a ring optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄)alkyl, -NH₂, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, and -NO₂; or a pharmaceutically acceptable salt thereof.

14. (Original) A pharmaceutical composition of Claim 11 wherein R₇ and R₈ are concatenated together as -(CH₂)_p-, wherein p is an integer of from 2 to 6, preferably 4 to 6, the ring so formed is optionally substituted with 1-3 substituents selected from a group containing C₁-C₃ alkyl, trifluoromethyl, halogen, hydrogen, phenyl, nitro, -CN.

15. (Withdrawn) A pharmaceutical composition of Claim 4 wherein the active pharmacological agent is a compound of the formulae (V) or (VI):



wherein the variable substituents including R₁, R₂, R₃, R₄, R₅, R₆, n, X, and Y are as defined in Claim 7, or a pharmaceutically acceptable salt thereof.

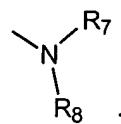
16. (Withdrawn) A pharmaceutical composition of Claim 15 wherein:
R₁ is selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, benzyloxy, or halogen;

R₂, R₃, R₅, and R₆ are independently selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, halogen, cyano, C₁-C₆ alkyl, or trihalomethyl, preferably trifluoromethyl, with the proviso that, when R₁ is H, R₂ is not OH;

R₄ is selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, benzyloxy, halogen, cyano, C₁-C₆ alkyl, or trihalomethyl;

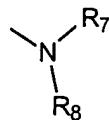
X is selected from H, C₁-C₆ alkyl, cyano, nitro, trifluoromethyl, halogen;

Y is the moiety



R₇ and R₈ are selected independently from H, C₁-C₆ alkyl, or combined by -(CH₂)_p-, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄), -NH₃, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, -NHSO₂(C₁-C₄), -NHCO(C₁-C₄), and -NO₃;
or a pharmaceutically acceptable salt thereof.

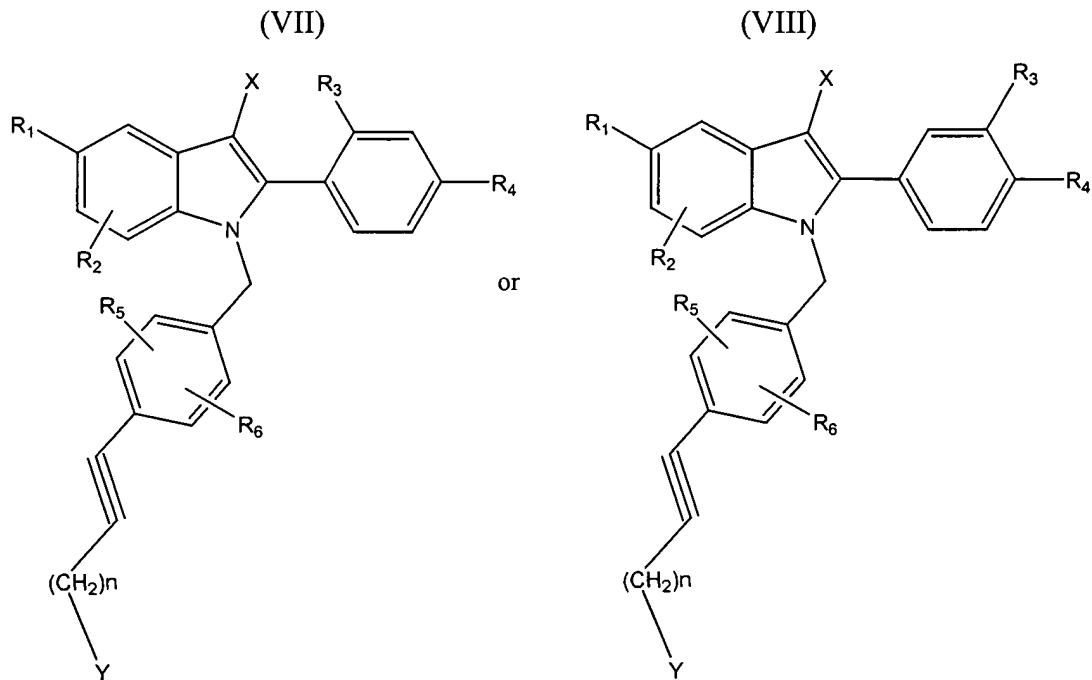
17. (Withdrawn) A pharmaceutical composition of Claim 15 wherein R₁ is OH; R₂ - R₆ are as defined above; X is selected from the group of Cl, NO₂, CN, CF₃, or CH₃; and Y is the moiety



and R₇ and R₈ are concatenated together as -(CH₂)_r-, wherein r is an integer of from 4 to 6, to form a ring optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄)alkyl, -NH₂, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, and -NO₂; or a pharmaceutically acceptable salt thereof.

18. (Withdrawn) A pharmaceutical composition of Claim 15 wherein R₇ and R₈ are concatenated together as -(CH₂)_p-, wherein p is an integer of from 2 to 6, preferably 4 to 6, the ring so formed is optionally substituted with 1-3 substituents selected from a group containing C₁-C₃ alkyl, trifluoromethyl, halogen, hydrogen, phenyl, nitro, -CN.

19. (Withdrawn) A pharmaceutical composition of Claim 4 wherein the active pharmacological agent is a compound of the formulae (VII) or (VIII):



wherein the variable substituents including R₁, R₂, R₃, R₄, R₅, R₆, n, X, and Y are as defined in Claim 7, or a pharmaceutically acceptable salt thereof.

20. (Withdrawn) A pharmaceutical composition of Claim 19 wherein:

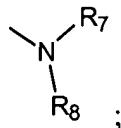
R₁ is selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, benzyloxy, or halogen;

R₂, R₃, R₅, and R₆ are independently selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, halogen, cyano, C₁-C₆ alkyl, or trihalomethyl, preferably trifluoromethyl, with the proviso that, when R₁ is H, R₂ is not OH;

R₄ is selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, benzyloxy, halogen, cyano, C₁-C₆ alkyl, or trihalomethyl;

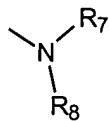
X is selected from H, C₁-C₆ alkyl, cyano, nitro, trifluoromethyl, halogen;

Y is the moiety



R₇ and R₈ are selected independently from H, C₁-C₆ alkyl, or combined by -(CH₂)_p, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄), -NH₃, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, -NHSO₂(C₁-C₄), -NHCO(C₁-C₄), and -NO₃;
or a pharmaceutically acceptable salt thereof.

21. (Withdrawn) A pharmaceutical composition of Claim 19 wherein R₁ is OH; R₂ - R₆ are as defined above; X is selected from the group of Cl, NO₂, CN, CF₃, or CH₃; and Y is the moiety



and R₇ and R₈ are concatenated together as -(CH₂)_r, wherein r is an integer of from 4 to 6, to form a ring optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄)alkyl, -NH₂, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, and -NO₂; or a pharmaceutically acceptable salt thereof.

22. (Withdrawn) A pharmaceutical composition of Claim 19 wherein R₇ and R₈ are concatenated together as -(CH₂)_p-, wherein p is an integer of from 2 to 6, preferably 4 to 6, the ring so formed is optionally substituted with 1-3 substituents selected from a group containing C₁-C₃ alkyl, trifluoromethyl, halogen, hydrogen, phenyl, nitro, -CN.

23. (Original) A pharmaceutical composition of Claim 4 wherein the active pharmacological agent is 1-[4-(2-Azepan-1yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol or a pharmaceutically acceptable salt thereof.

24. (Withdrawn) A pharmaceutical composition of Claim 4 wherein the active pharmacological agent is 2-(4-Hydroxy-phenyl)-3-methyl-1-(4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol or a pharmaceutically acceptable salt thereof.

25. (Original) A pharmaceutical composition of Claim 4 wherein the active pharmacological agent is selected from the group of raloxifene, tamoxifen, droloxitene, arzoxifene or CP 336156, or a pharmaceutically acceptable salt thereof.

26. (Original) A pharmaceutical composition comprising:

- a) a pharmaceutically effective amount of 1-[4-(2-Azepan-1yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol or 2-(4-Hydroxy-phenyl)-3-methyl-1-(4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol, or a pharmaceutically acceptable salt thereof;
- b) a filler and disintegrant component comprising between about 50% and about 80% of the formulation, with from about 4% to about 40% of the formulation comprising one or more disintegrant agents;

c) a wetting agent comprising between about 0.5% and about 2.5% of the formulation;

d) a lubricant comprising between about 0.2% and about 5% of the formulation; and

e) a glidant comprising between about 0.1% and about 5% of the formulation.

27. (Original) The pharmaceutical composition of Claim 26 further comprising an antioxidant at a concentration of from about 0.5% to about 5% by weight of the composition, the antioxidant being selected from the group of ascorbic acid, sodium ascorbate, ascorbyl palmitate, or mixtures thereof.

28. (Original) The pharmaceutical composition of Claim 26 further being coated with a film coating comprising from about 0.3% to about 8% by weight of the composition.

29. (Original) A pharmaceutical composition comprising:

a) a pharmaceutically effective amount of 1-[4-(2-Azepan-1yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol or 2-(4-Hydroxy-phenyl)-3-methyl-1-(4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol, or a pharmaceutically acceptable salt thereof;

b) a filler and disintegrant component of one or more pharmaceutically acceptable fillers and disintegrants comprising between about 54% and about 87% of the formulation, the disintegrants therein comprising from about 25% to about 35% of the formulation, by weight;

- c) a wetting agent comprising between about 0.55% and about 2.7% of the formulation;
- d) a lubricant comprising between about 0.2% and about 5.5% of the formulation; and
- e) a glidant comprising between about 0.1% and about 5.5% of the formulation.

30. (Original) The pharmaceutical composition of Claim 29 further comprising an antioxidant at a concentration of from about 0.5% to about 5% by weight of the composition, the antioxidant being selected from the group of ascorbic acid, sodium ascorbate, ascorbyl palmitate, or a mixture thereof.

31. (Original) The pharmaceutical composition of Claim 29 further being coated with a film coating comprising from about 0.3% to about 8% by weight of the composition.

32. (Original) A pharmaceutical composition comprising, by weight:

- a) from about 2% to about 8% 1-[4-(2-Azepan-1yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol or 2-(4-Hydroxy-phenyl)-3-methyl-1-(4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol, or a pharmaceutically acceptable salt thereof;
- b) lactose from about 32% to about 38%;
- c) microcrystalline cellulose from about 32% to about 38%;
- d) pregelatinized starch from about 12% to about 16%;
- e) ascorbic acid from about 1% to about 2%;
- f) sodium lauryl sulfate from about 1% to about 2%;
- g) sodium starch glycolate from about 4% to about 8%;
- h) silicon dioxide from about 0.1% to about 0.2%; and
- i) magnesium stearate from about 0.3% to about 0.7%.

33. (Original) A pharmaceutical composition comprising, by weight:

- a) from about 0.1% to about 25% 1-[4-(2-Azepan-1yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol or 2-(4-Hydroxy-phenyl)-3-methyl-1-(4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol, or a pharmaceutically acceptable salt thereof;
- b) from about 20% to about 80% lactose;
- c) from about 4% to about 40% pregelatinized starch;
- d) from about 0.2% to about 5% sodium lauryl sulfate;
- e) from about 0.5% to about 15% ascorbic acid;
- f) from about 0.1% to about 10% silicon dioxide; and
- g) from about 0.2% to about 10% magnesium stearate.

34. (Original) A pharmaceutical composition of Claim 33 comprising, by weight:

- a) from about 5% to about 18% 1-[4-(2-Azepan-1yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol or 2-(4-Hydroxy-phenyl)-3-methyl-1-(4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol, or a pharmaceutically acceptable salt thereof;
- b) from about 47% to about 77% lactose;
- c) from about 25% to about 35% pregelatinized starch;
- d) from about 1% to about 2% sodium lauryl sulfate;
- e) from about 1% to about 3% ascorbic acid;
- f) from about 0.1% to about 0.5% silicon dioxide; and
- g) from about 0.2% to about 0.5% magnesium stearate.

35. (New) A pharmaceutical composition comprising:

- a) an active pharmacological agent from about 0.1% to about 25% by weight of the pharmaceutical formulation, wherein the active pharmacological agent is 1-[4-(2-Azepan-1yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol or a pharmaceutically acceptable salt thereof;
- b) a filler and disintegrant component comprising from about 20% to about 80% by weight of the pharmaceutical formulation;
- c) a disintegrant component comprising from about 4% to about 40% by weight of the pharmaceutical formulation;
- d) a wetting agent comprising from about 0.2% to about 5% of the pharmaceutical formulation;
- e) an antioxidant comprising from about 0.5% to about 15% of the pharmaceutical formulation;
- f) a glidant comprising from about 0.1% to about 10% of the pharmaceutical formulation; and
- g) a lubricant comprising from about 0.2% to about 10% of the pharmaceutical formulation.

36. (New) The pharmaceutical composition of claim 35 wherein the filler and disintegrant component comprises lactose and microcrystalline cellulose.

37. (New) The pharmaceutical composition of claim 35 wherein the disintegrant component comprises pregelatinized starch.

38. (New) The pharmaceutical composition of claim 35 wherein the filler and disintegrant component comprises lactose and microcrystalline cellulose; and the disintegrant component comprises pregelatinized starch.

39. (New) The pharmaceutical composition of claim 38 wherein the antioxidant comprises ascorbic acid.

40. (New) The pharmaceutical composition of claim 38 wherein the lubricant comprises magnesium stearate.

41. (New) The pharmaceutical composition of claim 38 wherein the antioxidant comprises ascorbic acid; and the lubricant comprises magnesium stearate.

42. (New) The pharmaceutical composition of claim 41 wherein the glidant comprises silicon dioxide; and the wetting agent comprises sodium lauryl sulfate.

43. (New) A pharmaceutical formulation containing a pharmaceutically effective amount of 1-[4-(2-Azepan-1yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol or a pharmaceutically acceptable salt thereof, and a carrier or excipient system comprising:

a) a filler and disintegrant component comprising between about 50% and about 87% of the formulation, with from about 4% to about 40% of the formulation comprising one or more disintegrant agents;

- b) a wetting agent comprising between about 0.5% and about 2.7% of the formulation;
- c) a lubricant comprising between about 0.2% and about 5.5% of the formulation; and
- d) a glidant comprising between about 0.1% and about 5.5% of the formulation.

44. (New) The pharmaceutical formulation of claim 43 wherein the filler and disintegrant component comprises lactose and microcrystalline cellulose.

45. (New) The pharmaceutical composition of claim 43 wherein one of the the disintegrant agents is pregelatinized starch.

46. (New) The pharmaceutical composition of claim 43 wherein the filler and disintegrant component comprises lactose and microcrystalline cellulose; and one of the disintegrant agents is pregelatinized starch.

47. (New) A pharmaceutical formulation containing a pharmaceutically effective amount of 1-[4-(2-Azepan-1yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol or a pharmaceutically acceptable salt thereof, and a carrier or excipient system comprising:

- a) a filler and disintegrant component comprising between about 50% and about 87% of the formulation;
- b) one or more disintegrant agents comprising from about 4% to about 40% of the formulation;

- c) a wetting agent comprising between about 0.5% and about 2.7% of the formulation;
- d) a lubricant comprising between about 0.2% and about 5.5% of the formulation; and
- e) a glidant comprising between about 0.1% and about 5.5% of the formulation.

48. (New) The pharmaceutical formulation of claim 47 wherein the filler and disintegrant component comprises lactose and microcrystalline cellulose.

49. (New) The pharmaceutical composition of claim 47 wherein the disintegrant agents comprise pregelatinized starch and sodium starch glycolate.

50. (New) The pharmaceutical composition of claim 47 wherein the filler and disintegrant component comprises lactose and microcrystalline cellulose; and the disintegrant agents comprise pregelatinized starch and sodium starch glycolate.

51. (New) The pharmaceutical composition of claim 50 wherein the wetting agent comprises sodium lauryl sulfate.

52. (New) The pharmaceutical composition of claim 50 wherein the lubricant comprises magnesium stearate.

53. (New) The pharmaceutical composition of claim 50 wherein the glidant comprises silicon dioxide.

54. (New) The pharmaceutical composition of claim 50 wherein the wetting agent comprises sodium lauryl sulfate, the lubricant comprises magnesium stearate, and the glidant comprises silicon dioxide.

55. (New) The pharmaceutical carrier or excipient system of claim 1 wherein the filler and disintegrant component comprises lactose and microcrystalline cellulose; and the pharmaceutically acceptable disintegrants comprise pregelatinized starch and sodium starch glycolate.

56. (New) The pharmaceutical carrier or excipient system of claim 2 wherein the filler and disintegrant component comprises lactose and microcrystalline cellulose; and the pharmaceutically acceptable disintegrants comprise pregelatinized starch and sodium starch glycolate.

57. (New) The pharmaceutical carrier or excipient system of claim 3 wherein the filler and disintegrant component comprises lactose and microcrystalline cellulose; and the pharmaceutically acceptable disintegrants comprise pregelatinized starch and sodium starch glycolate.

58. (New) The pharmaceutical composition of claim 4 wherein the filler and disintegrant component comprises lactose and microcrystalline cellulose; and the pharmaceutically acceptable disintegrants comprise pregelatinized starch and sodium starch glycolate.

59. (New) The pharmaceutical composition of claim 5 wherein the filler and disintegrant component comprises lactose and microcrystalline cellulose; and the pharmaceutically acceptable disintegrants comprise pregelatinized starch and sodium starch glycolate.

60. (New) The pharmaceutical composition of claim 6 wherein the filler and disintegrant component comprises lactose and microcrystalline cellulose; and the pharmaceutically acceptable disintegrants comprise pregelatinized starch and sodium starch glycolate.

61. (New) The pharmaceutical carrier or excipient system of claim 1 wherein the filler and disintegrant component consists of lactose and microcrystalline cellulose; and the pharmaceutically acceptable disintegrants are pregelatinized starch and sodium starch glycolate.

62. (New) The pharmaceutical carrier or excipient system of claim 2 wherein the filler and disintegrant component consists of lactose and microcrystalline cellulose; and the pharmaceutically acceptable disintegrants are pregelatinized starch and sodium starch glycolate.

63. (New) The pharmaceutical carrier or excipient system of claim 3 wherein the filler and disintegrant component consists of lactose and microcrystalline cellulose; and the pharmaceutically acceptable disintegrants are pregelatinized starch and sodium starch glycolate.

64. (New) The pharmaceutical composition of claim 4 wherein the filler and disintegrant component consists of lactose and microcrystalline cellulose; and the pharmaceutically acceptable disintegrants are pregelatinized starch and sodium starch glycolate.

65. (New) The pharmaceutical composition of claim 5 wherein the filler and disintegrant component consists of lactose and microcrystalline cellulose; and the pharmaceutically acceptable disintegrants are pregelatinized starch and sodium starch glycolate.

66. (New) The pharmaceutical composition of claim 6 wherein the filler and disintegrant component consists of lactose and microcrystalline cellulose; and the pharmaceutically acceptable disintegrants are pregelatinized starch and sodium starch glycolate.

Claims 1-14, 23, and 25-34 are pending in this application. Claims 15-22 and 24 are withdrawn from consideration. Claims 35 through 66 are new. Support for new claims 35-66 can be found, for example, in Example 2, on pages 27-28 of the specification, and on page 25, lines 4-16 of the specification.

Claims 1-14, 23, and 25-34 stand rejected under 35 U.S.C. § 103(a) for alleged obviousness over Miller et al. (5,780,497, or 5,880,137, or EP 0802184 A1, or EP 0802183 A1; collectively “Miller et al.”) in view of Sawicka (Pharmazie 1991, vol. 46 page 519-521). Applicants respectfully traverse the rejection, as the cited art neither teaches nor suggests the subject matter of the pending claims.

The Office Action asserts that Miller et al.:

... teaches broadly a pharmaceutical carrier or excipient system in a pharmaceutical formulation comprising a filler and disintegrant components, a wetting agent, a lubricant, and a glidant including the instant preferred excipients such as lactose, microcrystalline cellulose, magnesium stearate and sulfate, and Miller et al. teaches that the preparation of the formulation comprising the instant compound in various oral forms with these well known excipients is conventional to an ordinary skilled artisan in pharmaceutical science.

The Office Action at page 3. Significantly, the Office Action admits that the prior art does not expressly disclose the claimed specific range amounts of a filler and disintegrant components, a wetting agent, a lubricant, and a glidant in a pharmaceutical composition, and also that the prior art does not expressly disclose the claimed pharmaceutical composition further comprising an antioxidant. The Office Action nevertheless repeats its assertion that it would have been obvious:

...to determine the specific range amounts of a filler and disintegrant components, a wetting agent, a lubricant, and a glidant in a pharmaceutical composition herein, and to further add an antioxidant to a pharmaceutical composition herein.

Office Action at page 3. The Office Action bases its conclusion on an assertion that the components of the claimed formulations are known in the art, and that the determination and optimization of amounts of such components are considered conventional, relying on *In re Boesch*, 205 USPQ 215 (CCPA 1980).

As best understood, the Office Action appears to assert that where compounds and formulation ingredients are known in the art then, *a priori*, any formulation developed therefrom is *prima facie* obvious under *In re Boesch*, which, according to the Office Action, holds that it is within the skill in the art to select optimal parameters, such as the amount of ingredients, in order to achieve a beneficial effect. However, the court in *In re Boesch* upheld the Board's finding of Applicant's invention to be *prima facie* obvious, at least in part, because the ranges of Applicant's claimed invention overlapped with those of the prior art. See *In re Boesch*, at 218 ("The board agreed with the examiner that the claimed alloys were *prima facie* obvious from the prior art, noting that there was no substantial disagreement that both Pohlman et al. and Lamb disclose alloys *having compositional limits overlapping those of the claimed alloys.*") (emphasis added).

The facts of *In re Boesch* stand in stark contrast to the present application wherein a large number of possible parameters that may or may not affect the outcome must be correctly chosen, discarded or optimized without the guidance of any given ranges or other teachings from the art itself.¹ The Office Action appears to premise its argument on an assertion that it would be obvious for one of ordinary skill in the art to vary every possible parameter (and combinations of parameters) of a system in order to optimize the effectiveness of the system; even where there is no evidence in the record that any given parameter would affect the result. However, the Office Action has not pointed to any legally sufficient motivation to modify the cited art either by making the claimed selections of components, or by employing the claimed ranges of those components. At best, the Office Action has employed an "obvious to try" analysis,

¹ The Office Action asserts on page 5 that: "The teachings of Miller et al. regarding that making various formulations comprising the instant compound and those well known excipients is known to be conventional, clearly supporting the Examiner's position in the rejection" (Page 5, Office Action). However, Applicants do not find any support for the assertion in the cited art. The only references to conventional with regard to formulation in Miller et al can be seen, for example, in US 5,880,137 column 7, lines 28-31 ("Oral formulations containing the active compounds of this invention may comprise any *conventionally* (ital. added) used oral forms, including tablets, capsules, buccal forms troches, lozenges and oral liquids, suspensions, or solutions" and in US 5,880,137 column 7, lines 37-38 ("Useful tablet formulations may be made by *conventional* (ital. added) compression, wet granulation or dry granulation..."). Neither of these terms can be read as supporting the Office Action's position as quoted from page 5 of the office action.

which is not a permissible basis for a rejection under 35 U.S.C. §103. *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987).

The Office Action states on page 5 that Examples 1-9 of the specification are “not deemed persuasive as to the nonobviousness and/or unexpected results of the claimed invention over the prior art,” apparently on the basis that the specification provides no “side-by-side comparison with the closest prior art in support of nonobviousness for the instant claimed invention over the prior art.” However, this begs the question of what the examples of the subject application are supposed to be compared to. There are no formulation examples provided in Miller et al. (the closest prior art) to compare to, no matrix combinations to consider, no ranges to examine. Rather, Miller et al., at best, provides a “laundry list” of possible ingredients that may or may not be used in any possible combination and range. The inability to even draw a basis for comparison from Miller et al only further serves to highlight the reference’s inadequacy for supporting the present obviousness rejection.

The Office Action further alleges that the evidence in the specification is not “clear and convincing” (emphasis in original) in support of the nonobviousness of the instant claimed invention. However, Applicants respectfully point out that it is the Office that has the burden to set forth a *prima facie* case of obviousness (and Applicants assert that the Office Action has failed to do this in the present instance), and that Applicants do not have to demonstrate unexpected results in the absence of such a case.²

² Moreover, the Office Action’s “clear and convincing” evidence standard is incorrect. MPEP section 716.01(d) clearly states that:

“The ultimate determination of patentability must be based on consideration of the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence.”

While hastening to reiterate that secondary considerations of nonobviousness are not required in the absence of a *prima facie* case of obviousness, and that no such *prima facie* case has been made in the present Office Action, Applicants re-emphasize that even where a *prima facie* case of obviousness has been made, Applicant’s overall burden is to establish nonobviousness by a *preponderance of the evidence* in light of the entire record.

The Office Action further asserts that the inclusion of an antioxidant into formulations containing compounds of the present invention is obvious from Miller et al. in view of Sawicka, apparently on the basis that Sawicka allegedly teaches that:

... adding an antioxidant to a pharmaceutical composition is well known in the art and the stability of a pharmaceutical composition may be increase [sic] by antioxidant addition."

Office Action at page 3. However, Sawicka does not teach that addition of an antioxidant to a pharmaceutical composition is well known in the art. Rather, Sawicka refers to the problem of vitamin (D₂ and D₃) stability in solid dosage form, and also teaches that the stability issues of vitamin D (D₂ and D₃) has been known for some time and has been addressed in numerous publications. Sawicka does not teach the general applicability of antioxidants for compounds other than vitamin D₃, and nowhere in either of the cited references is it taught or suggested that antioxidants are a solution to drug decomposition regardless of chemical structure, formulation make-up, etc. Indeed, those of skill in the art recognize that antioxidants are molecules that interact differently depending upon environmental influences, the compounds that they are protecting, and the matrix in which they are included. Accordingly, it cannot be said that the Sawicka reference teaches or suggests that adding an antioxidant or combination of antioxidants to compounds such as those of the present claims will result in the benefits disclosed by Applicants with a reasonable expectation of success. Further, neither Sawicka nor Miller et al., or the combination thereof, teaches or suggests the desirability of adding an antioxidant or combination of antioxidants to the compounds of the present application. Thus, it cannot be said that one of skill in the art would be motivated to try an antioxidant from the disclosure of Sawicka which uses nonanalogous compounds in nonanalogous formulations, with a reasonable expectation of success. Accordingly, the cited art, alone or in combination, does not render the present claims obvious.

DOCKET NO.: WYTH 0011-100

PATENT

In view of the foregoing, Applicants assert that the pending claims are in condition for allowance, and an early Office Action to that effect is earnestly solicited.

Respectfully submitted,

Chris P. Miller
Registration No. 55,852

Chris Miller
Michael P. Straher
Registration No. 38,325

Date: February 27, 2004

COZEN O'CONNOR
1900 Market Street
Philadelphia, PA 19103
Tel: (215) 665-5548